

FDA Overview

BLA 761074

**MYL-1401O, a proposed biosimilar to
US-licensed Herceptin**

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July 13, 2017

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Proposed Indications

Same as US-licensed Herceptin:

Adjuvant Breast Cancer

HER2 overexpressing node positive or node negative breast cancer:

- as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
- with docetaxel and carboplatin
- as a single agent following multi-modality anthracycline based therapy.

Metastatic Breast Cancer

- in combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
- as a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

***Metastatic Gastric Cancer**

- in combination with cisplatin and capecitabine or 5-fluorouracil for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease

* Herceptin's gastric cancer indication is protected by orphan drug exclusivity expiring on October 20, 2017

Key Topics for Discussion

1. Please discuss whether the evidence supports a demonstration that “MYL-1401O” is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components.
2. Please discuss whether the evidence supports a demonstration that there are no clinically meaningful differences between “MYL-1401O” and US-Herceptin in the studied condition of use.
3. Please discuss whether there is adequate scientific justification to support licensure for all of the proposed indications.

Voting Question

- Does the totality of the evidence support licensure of MYL-1401O as a biosimilar product to US-Herceptin for the following indications for which US-Herceptin is licensed and for which Mylan is eligible for licensure (HER2 positive breast cancer in adjuvant and metastatic settings)?

Product Quality

Kristen Nickens, PhD

Product Quality Reviewer, Office of Biotechnology Products
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Meiyu Shen, PhD

CMC Statistical Reviewer, Office of Biostatistics
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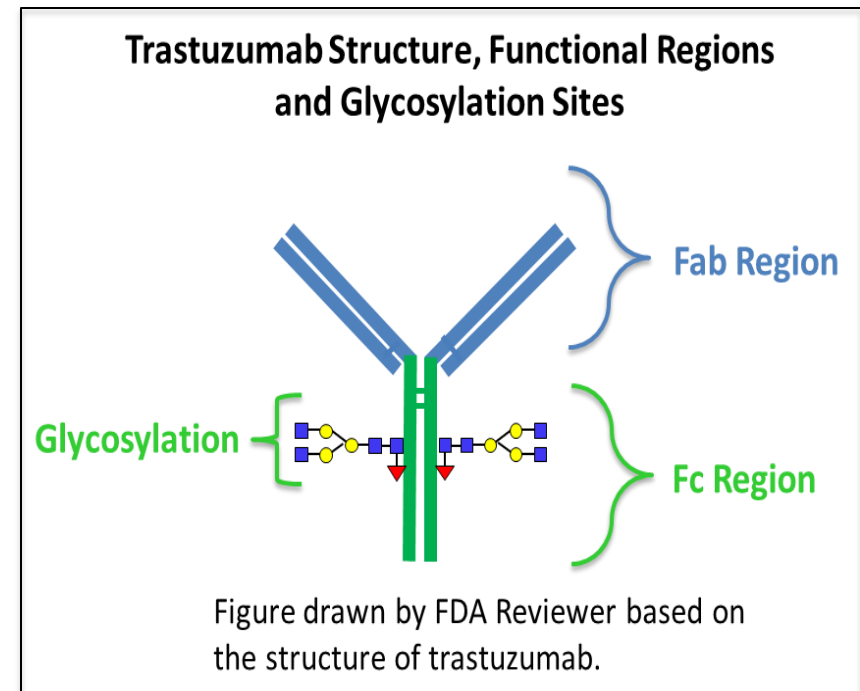
Trastuzumab Structure and Mechanisms of Action (MOA)



- Humanized immunoglobulin 1 (IgG1) kappa-isotype monoclonal antibody.
- Cellular target is the extracellular juxtamembrane domain of the human epidermal growth factor receptor 2 (HER2); a regulator of cellular survival pathways.

MOA:

- **Inhibition of HER2 receptor dimerization**
- **Increased destruction of the endocytic portion of the HER2 receptor**
- **Inhibition of HER2 extracellular domain shedding**
- **Inhibition of proliferation**
- **Effector function, including antibody-dependent cellular cytotoxicity (ADCC) and potentially ADC phagocytosis (ADCP)**



Fab – Fragment with specific antigen binding
Fc – Fragment crystallizable

Quality Attributes Evaluated



Quality Attribute	
Primary Structure	Amino acid sequence
	Molecular mass
Higher Order Structure	Secondary structure
	Tertiary structure
	Disulfide bonds
	Free thiols
Functional Activity	Target binding (HER2)
	Inhibition of proliferation
	Antibody-dependent cellular cytotoxicity (ADCC)
	Fc-receptor binding (FcRn, Fcγ-receptors)
	Cellular dependent cytotoxicity (CDC) bioassay (C1q-binding)
Product-related species	High molecular weight species
	Fragments
	Charge species (deamidation, isomerization, c-terminal lysine)
	Oxidation (Methionine)
	Hydrophobic species
	Cation exchange chromatography
	N-glycan occupancy and profile
Glycosylation	Afucosylation
	High mannose
	Sialic acid
	Terminal galactose
	Non-glycosylated
	Glycation
Drug Product attributes	Content
	Sub-visible particles
Stability	Thermal stability (accelerated and stressed), forced degradation

Orthogonal methods were used to assess most attributes.

FcRn – Neonatal Fc receptor
C1q – Complement receptor 1q

Product Lots and Data Analysis



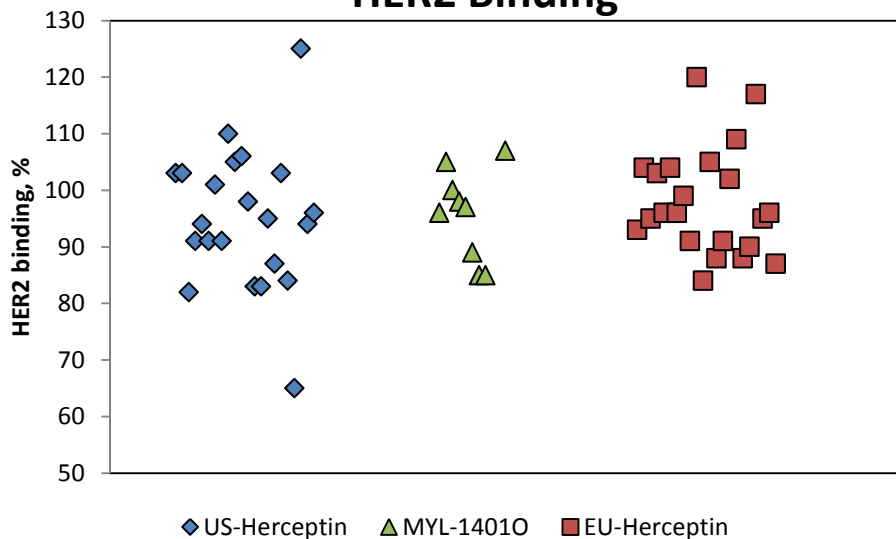
Product	Number of lots	Attribute Assessment	Statistical tools
MYL-1401O	16	Tier 1	Equivalence testing
US-Herceptin	28	Tier 2	Quality ranges
EU-Herceptin	38	Tier 3	Graphical comparison

- The analytical similarity program included:
 - Analytical comparisons between MYL-1401O and US-Herceptin
 - Analytical comparisons between MYL-1401O, US-Herceptin and EU-Herceptin to establish the analytical portion of the three-way scientific bridge
- The analytical similarity assessment included product lots used in the clinical studies and those manufactured by the proposed commercial process.
- The Applicant's comparative analysis was supported by statistical analysis.
- The FDA's evaluation also included independent statistical analysis.

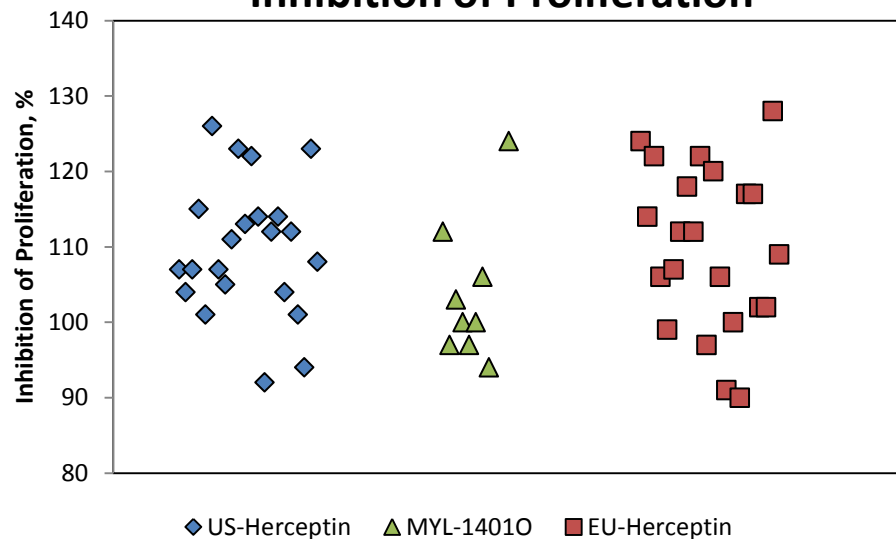
Functional Assays



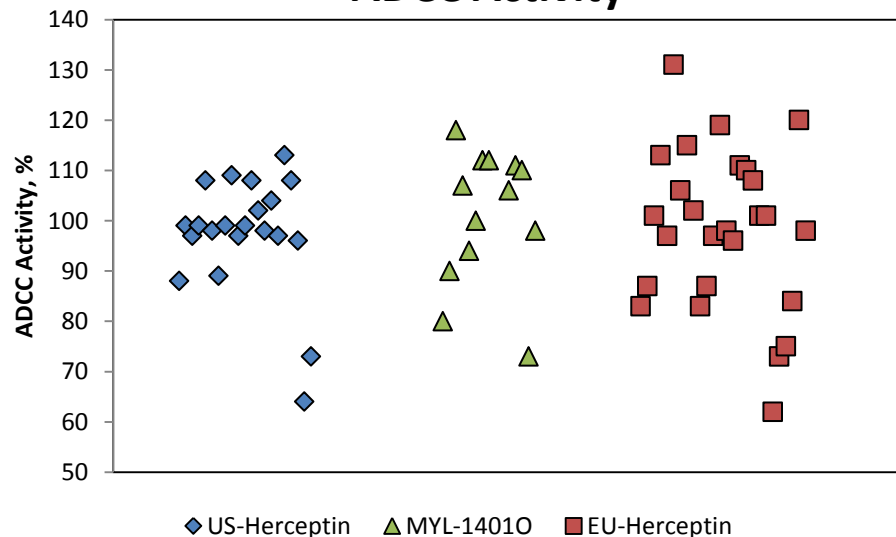
HER2 Binding



Inhibition of Proliferation



ADCC Activity

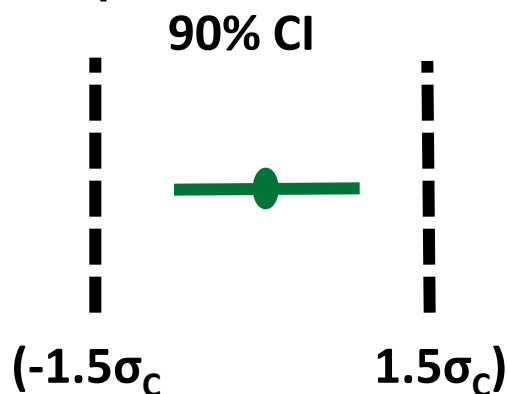


- HER2 binding, inhibition of proliferation, and ADCC activity were evaluated as Tier 1 quality attributes and statistically analyzed by equivalence testing.

Statistical Equivalence Test

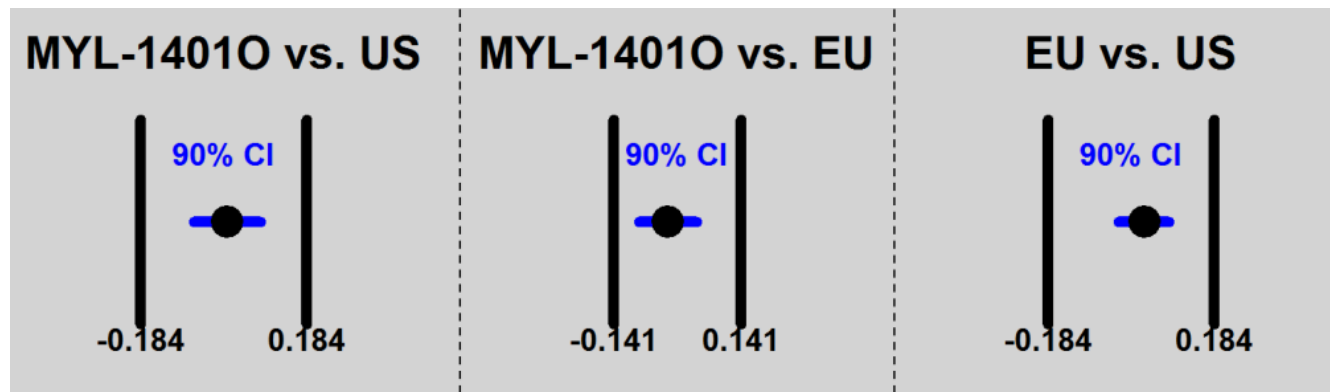
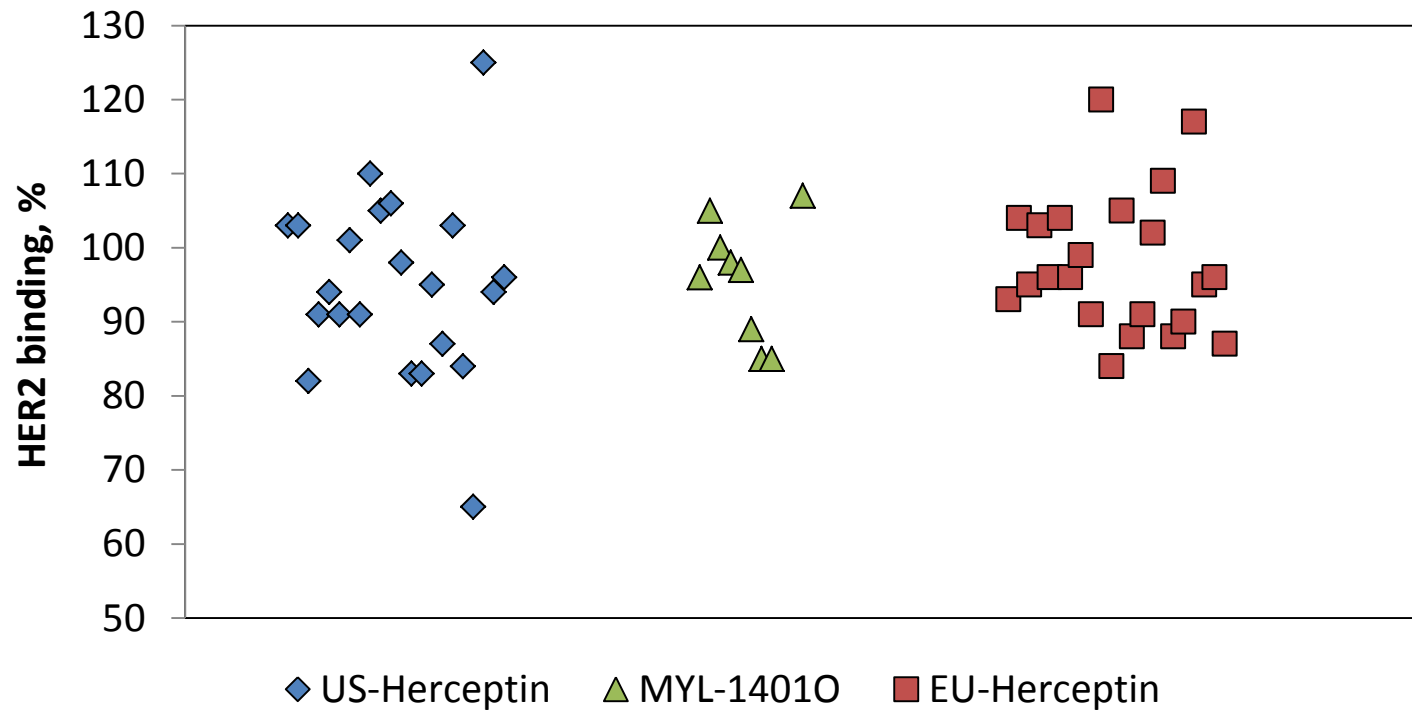


- Hypotheses:
 - H_0 : $\text{Mean}(\text{Test}) - \text{Mean}(\text{Comparator}) \geq 1.5\sigma_C$ or $\text{Mean}(\text{Test}) - \text{Mean}(\text{Comparator}) \leq -1.5\sigma_C$
 - H_a : $-1.5\sigma_C < \text{Mean}(\text{Test}) - \text{Mean}(\text{Comparator}) < 1.5\sigma_C$
- Test and comparator are equivalent if

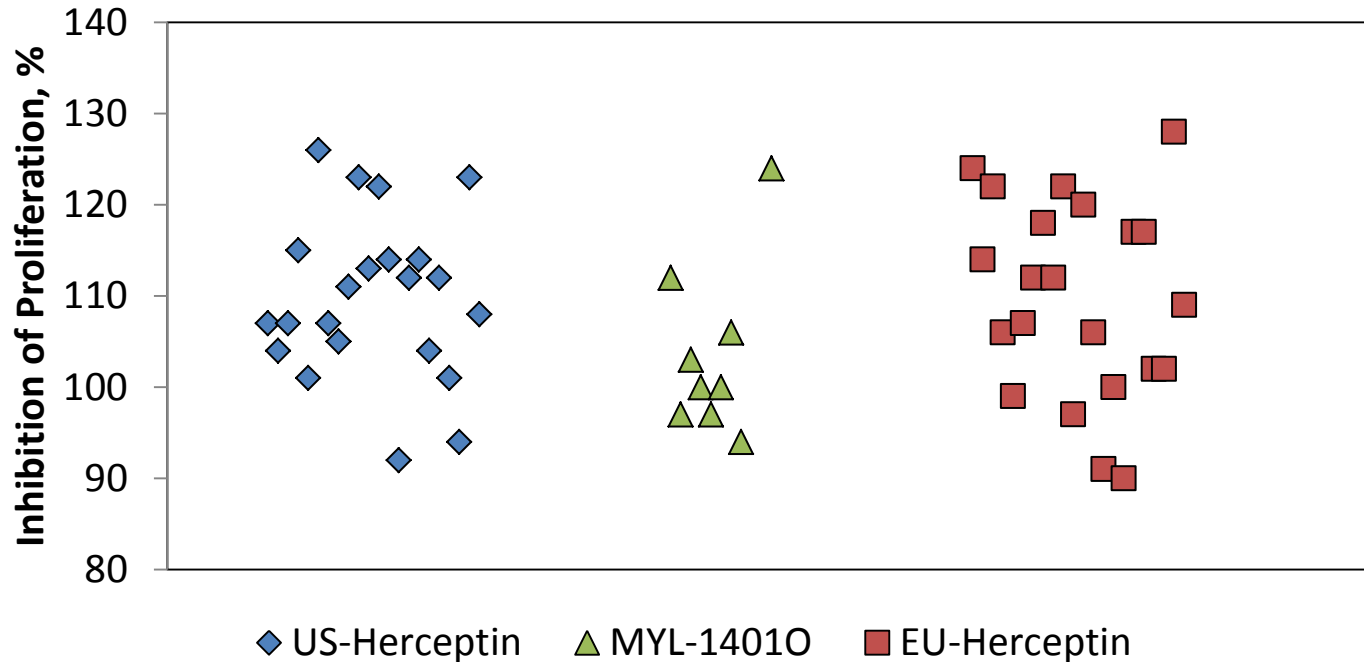


- Equivalence margin = $1.5\sigma_C$:
 - σ_C is estimated from comparator data generated by the applicant.

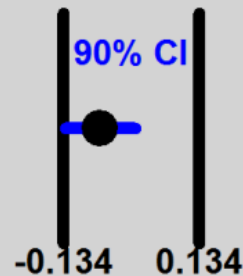
HER2 Binding



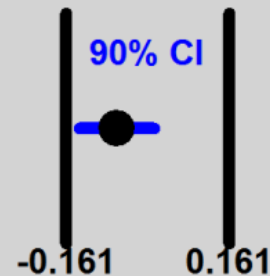
Inhibition of Proliferation



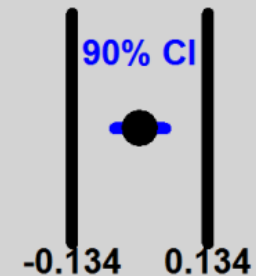
MYL-1401O vs. US



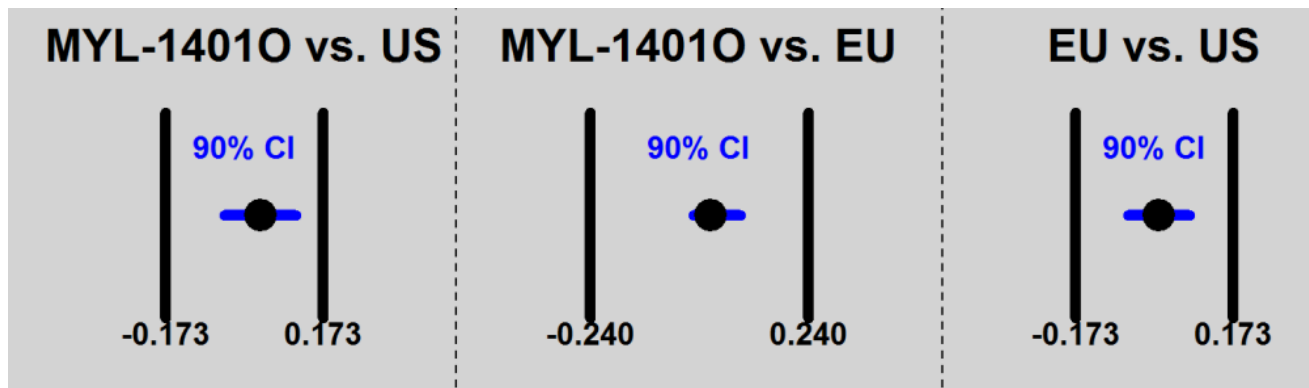
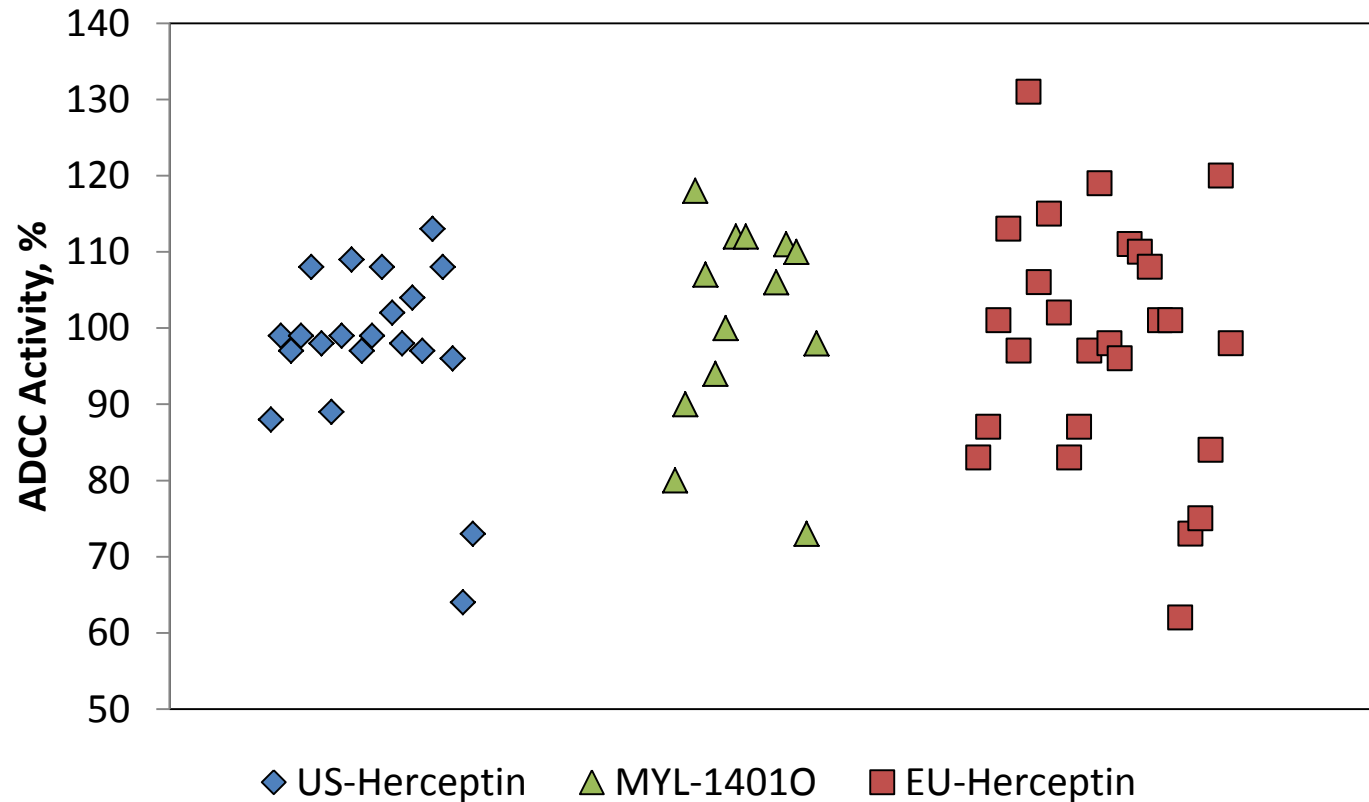
MYL-1401O vs. EU



EU vs. US



ADCC Activity



Equivalence Testing Summary

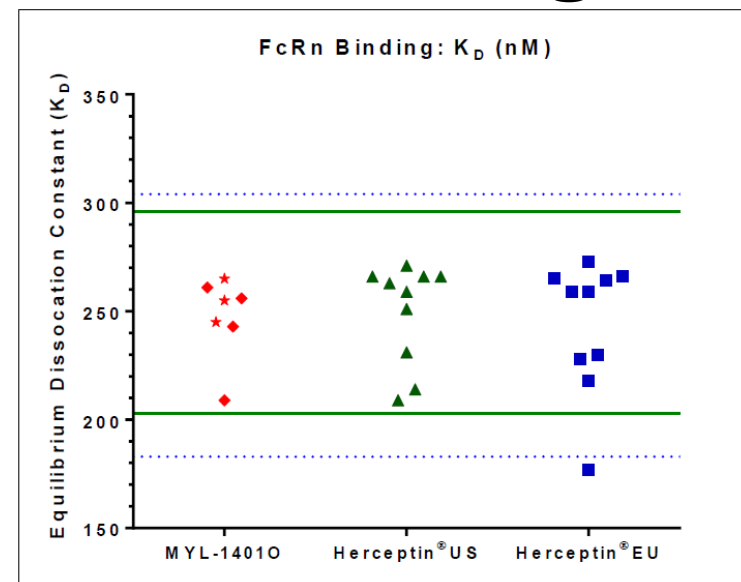
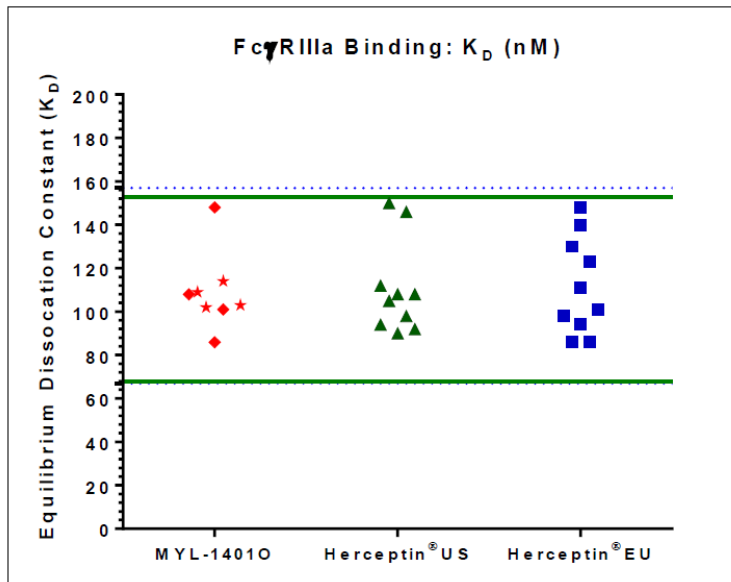


- HER2 Binding
 - All 3-way comparisons pass equivalence testing.

- Inhibition of Proliferation
 - All 3-way comparisons pass equivalence testing.

- Relative ADCC Activity
 - All 3-way comparisons pass equivalence testing.

FcγRIIIa and FcRn Binding



US-Herceptin-based quality range criteria are depicted by the green lines, and the EU-Herceptin-based quality range criteria are depicted by the dotted blue lines.

- FcγRIIIa and FcRn binding contribute to effector function and PK.
- MYL-1401O FcγRIIIa and FcRn binding kinetics are similar to US-Herceptin and EU-Herceptin.
- Binding to other Fc receptors can also stimulate effector functions; therefore, binding to additional Fc receptors (FcγRIa, FcγRIIa, FcγRIIb/c, FcγRIIIb) was evaluated, and similar binding kinetics among MYL-1401O, US-Herceptin, and EU-Herceptin were observed.

Analytical Similarity Summary

Quality Attribute	Supports Demonstration of Highly Similar	Quality Attribute	Supports Demonstration of Highly Similar
Primary Structure	Yes	Overall Glycosylation	Yes
Secondary & Tertiary Structure	Yes	Total Afucose	Yes
Potency - HER 2 Binding	Yes	Total Galactose	Yes
Potency – Inhibition of Proliferation	Yes	Total Mannose	Yes#
Potency – ADCC	Yes	Total Non-glycosylated Heavy Chain	Yes#
Protein Content	Yes	Total Sialic Acid	Yes#
Size variants and Aggregates	Yes	Fc Receptor Binding	Yes
Fragments	Yes	FcRn Binding	Yes
Charge and Hydrophobic variants	Yes#	CDC	Yes
		Sub-visible particles	Yes
		Stability profiles	Yes

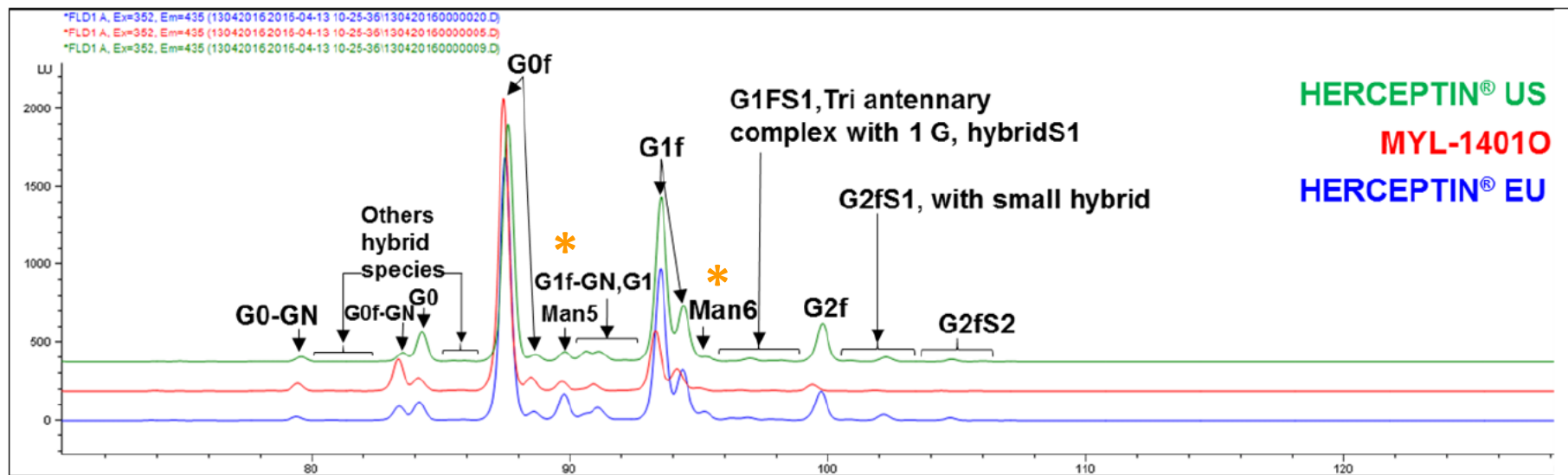
Minor differences in the levels of some glycosylation species and charge species did not preclude a demonstration that MYL-1401O is highly similar to US-Herceptin.

Glycosylation Profile



- MYL-1401O, US-Herceptin and EU-Herceptin have the same glycosylation sites, occupancy and species.
- Minor differences were observed in the content of some species.

Overlays of Native Glycans

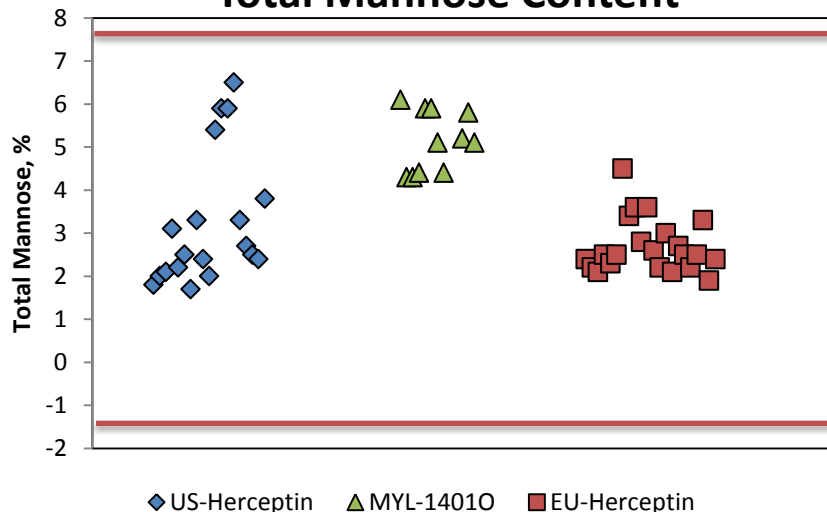


* Indicates differences in glycoform content among the three products

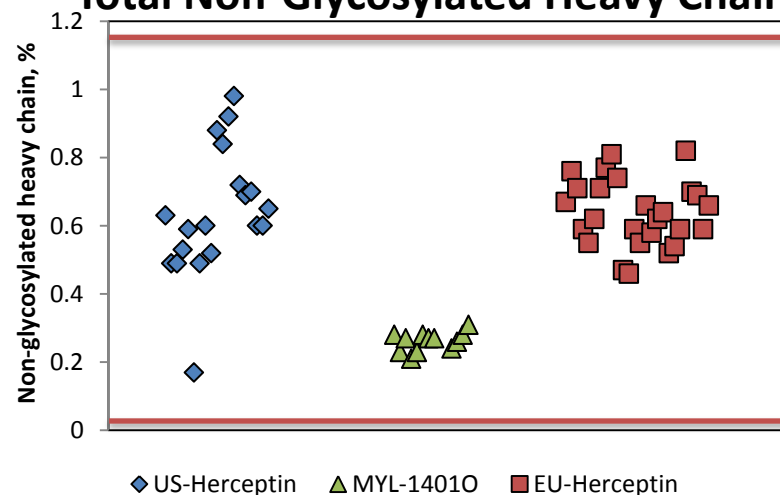
Figure excerpted from Applicant's 351(k) BLA submission

Glycan Species with Differences in Content

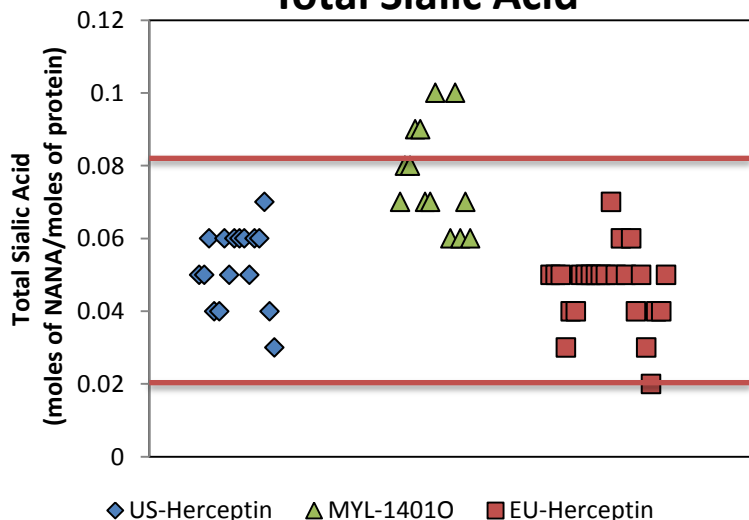
Total Mannose Content



Total Non-Glycosylated Heavy Chain



Total Sialic Acid



- MYL-14010 total mannose and non-glycosylated heavy chain content pass the quality criteria, but MYL-14010 generally has higher levels of total mannose and lower levels of non-glycosylated heavy chain compared to US-Herceptin and EU-Herceptin.
- For sialic acid, 31% of MYL-14010 lots were outside the US-based quality criteria.

US-Herceptin-based quality range criteria are depicted by the red lines.

Addressing Differences in Glycosylation

- Mannose and sialic acid can impact the pharmacokinetics (PK) of the molecule.
- A lack of glycosylation in the Fc region of the heavy chain of an antibody is correlated with loss of effector function.
- The potential impact of the glycosylation differences on biological activity were primarily evaluated with respect to ADCC activity using a cell-based bioassay and Fc receptor binding kinetics.
- The differences were adequately addressed by data showing no impact on ADCC activity, Fc receptor binding, or PK.

Addressing Differences in Charge Species

- MYL-1401O lots were within the quality range criteria for acidic and basic species.
- The main peak content of a single MYL-1401O lot was higher than the US-Herceptin quality criteria; these results were within the expectation for the proportion of lots meeting the quality range criterion for a tier 2 attribute.
- MYL-1401O lots generally had lower levels of acidic species and higher levels of main peak compared to US-Herceptin and EU-Herceptin.

Charge Species	MYL-1401O (mean, %)	US-Herceptin (mean, %)	EU-Herceptin (mean, %)
Acidic	25.6	30.6	28.4
Main	63.9	58.9	61.7
Basic	10.5	10.5	9.9

Addressing Differences in Charge Species

- The differences in charge species were correlated to differences in levels of deamidation at light chain asparagine 30, which is located in the HER2 binding region of trastuzumab.
- The deamidation levels are slightly higher in US-Herceptin and EU-Herceptin compared to MYL-1401O; this may be related to different ages of the materials.
- Characterization studies evaluating ADCC activity of the deamidated charged species were conducted to determine the potential impact of the differences on biological activity.
- The data show that the differences in acidic species have minimal effect on target binding and potency.
- These differences are not expected to have clinical impact.

CMC Conclusions

The totality of the analytical similarity data supports a conclusion that MYL-1401O is highly similar to US-Herceptin notwithstanding minor differences in clinically inactive components.

Clinical Pharmacology

Brian D. Furmanski, Ph.D.

Clinical Pharmacology Reviewer

Office of Clinical Pharmacology
U.S. Food and Drug Administration

Clinical Pharmacology Overview



The clinical pharmacology program aims to support the demonstration of no clinically meaningful differences between MYL-1401O and US-Herceptin by:

- Evaluating the single-dose pharmacokinetic (PK) similarity between MYL-1401O and US-Herceptin, and
- Establishing the PK portion of the scientific bridge between MYL-1401O, US-Herceptin, and EU-Herceptin

Clinical Studies

Study	Population	Design	Primary Endpoint	Dosing
MYL-HER-1002	Healthy subjects (120)	3-arm, parallel-group study of MYL-1401O, EU-Herceptin, and US-Herceptin	PK similarity	Single dose 8 mg/kg IV
MYL-HER-3001	Untreated metastatic HER2 positive breast cancer ITT1 (458) Safety (493)	Multicenter, randomized, double-blind, parallel-group Study of MYL-1401O and EU-Herceptin	Best ORR at week 24 by central review	Loading dose 8 mg/kg IV Maintenance dose 6 mg/kg Q3W with docetaxel 75 mg/m ² or paclitaxel 80 mg/m ² Q3W

ORR = Overall response rate

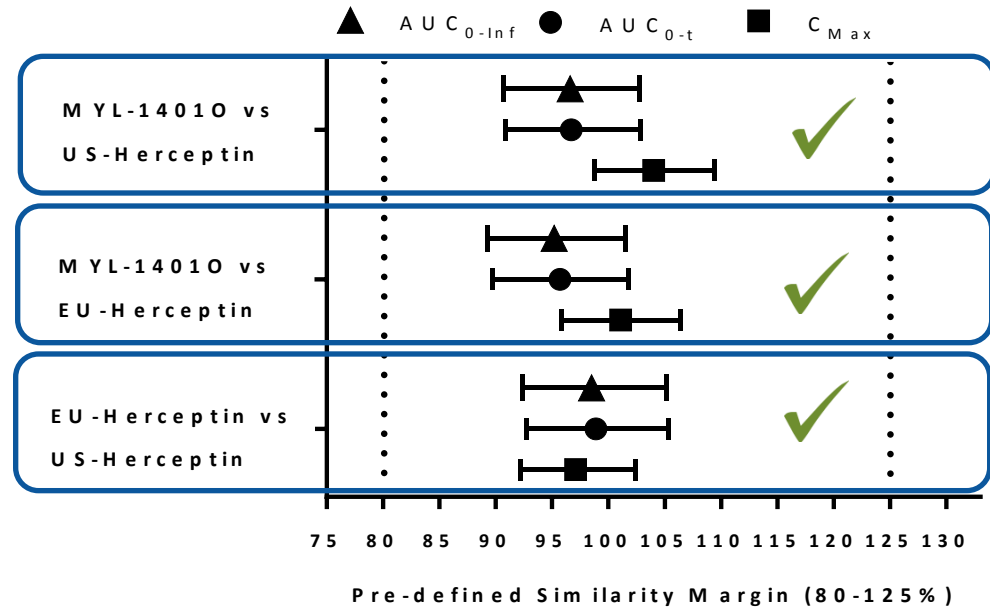
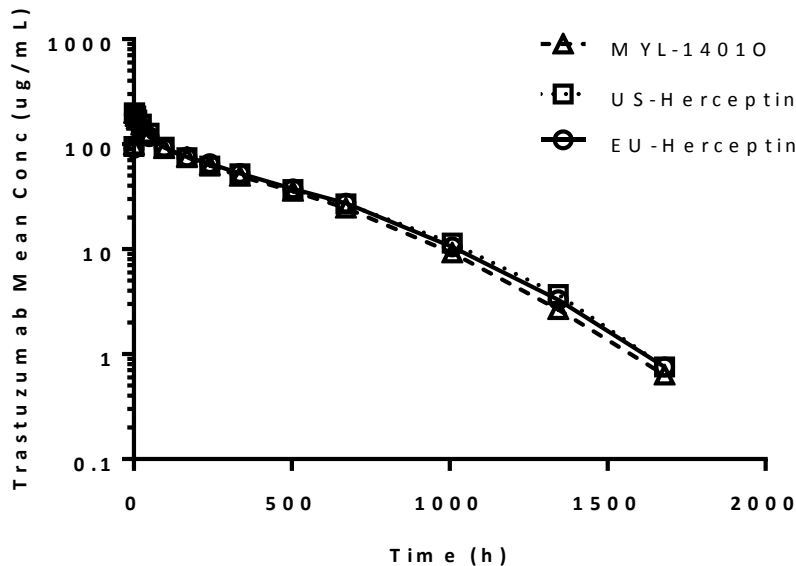
PK = Pharmacokinetic

ITT = Intention-to-treat

IV = intravenous

Study MYL-HER-1002

Demonstrated PK Similarity



- The geometric mean ratios and 90% confidence intervals are within the pre-specified 80-125% range

Clinical Pharmacology Summary



Results of MYL-HER-1002:

- Demonstrated PK similarity between MYL-1401O and US-Herceptin
- Established the PK portion of the scientific bridge between MYL-1401O, US-Herceptin, and EU-Herceptin
 - Justifies the relevance of the comparative clinical data generated using EU-Herceptin

Clinical Pharmacology Conclusion



- The PK results support a demonstration of no clinically meaningful differences between MYL-1401O and US-Herceptin, and add to the totality of the evidence to support a demonstration of biosimilarity of MYL-1401O and US-Herceptin

Clinical Efficacy and Safety

Jennifer Gao, MD

Medical Officer
Division of Oncology Products 1
U.S. Food and Drug Administration

Comparative Clinical Study

Study	Population	Design	Primary Endpoint	Dosing
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MYL-Her 3001 Study Design

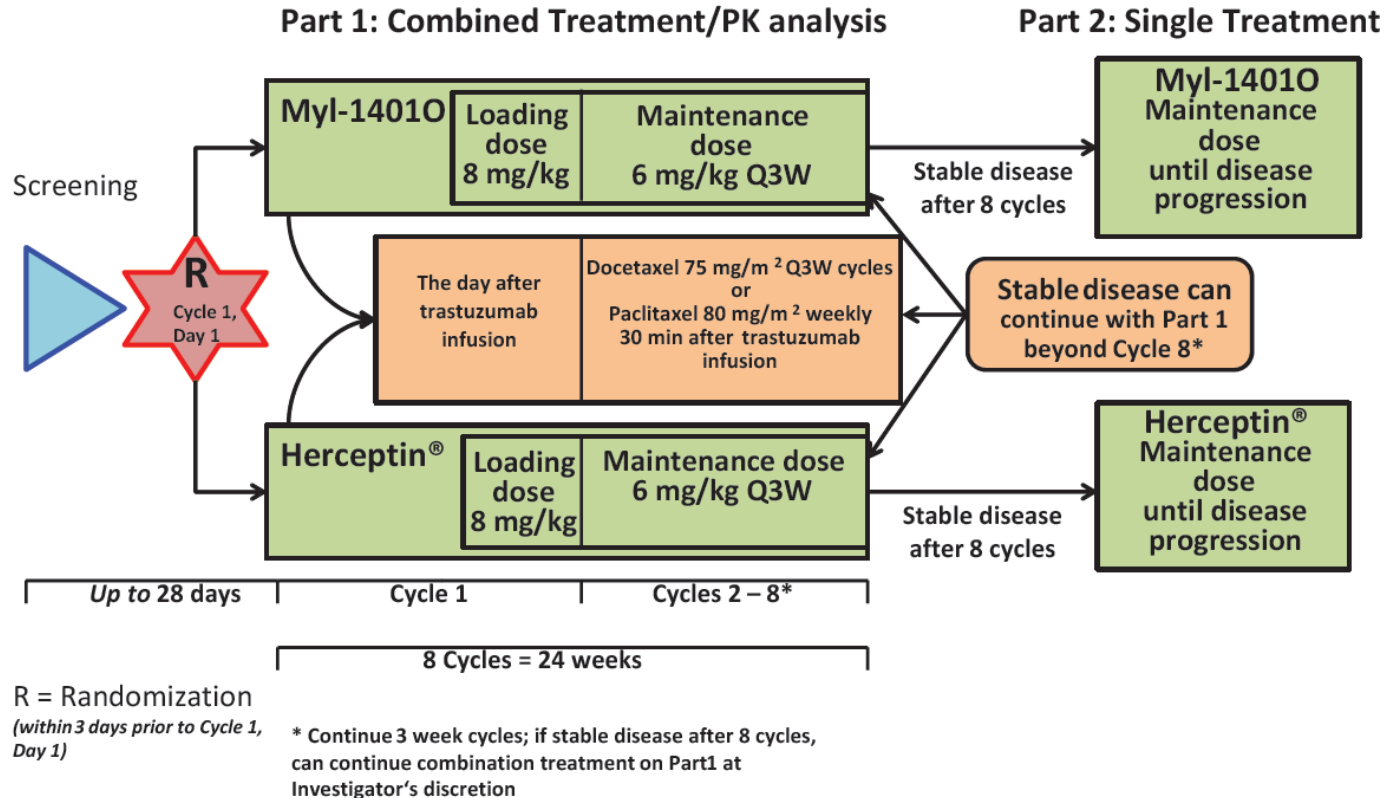
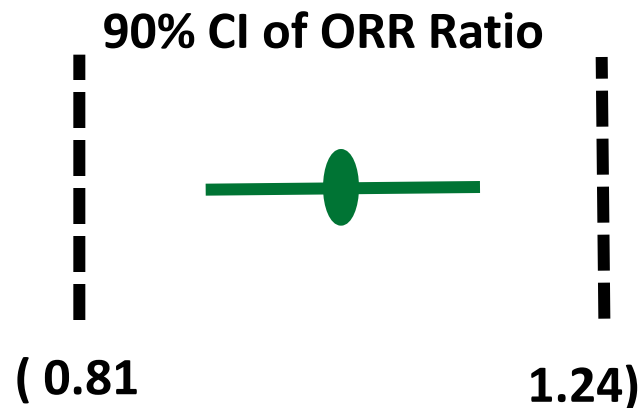


Figure excerpted from Applicant's 351(k) BLA submission

- **Primary analysis population:** all patients who were randomized to first-line treatment for metastatic breast cancer
- **Primary endpoint:** ORR at 24 weeks by Central Review

Equivalence Margin

- General considerations
 - Trial to resolve residual uncertainties
 - Margins to ensure no clinically meaningful difference
 - Trial to be feasible – sample size not based on establishing efficacy (i.e. non-inferiority or superiority)
- Equivalence margin per ORR ratio: (0.81, 1.24)
 - Corresponding to the absolute difference in ORR (-13%, 17%), assuming the reference product ORR of 69%
- MYL-1401O and EU-Herceptin are equivalent if:



Clinical Efficacy

	Primary Population	
	MYL-1401O (N=230)	EU-Herceptin (N=228)
ORR by central review, n (%)	161* (70%)	146 (64%)
ORR Ratio (90% CI)	1.09 (0.98, 1.22)	
ORR Difference (90% CI)	6% (-1.3%, 13.2%)	

**One patient with no measurable disease at baseline was determined as having a complete response per central review of non-target lesions. This patient was counted as a responder in the FDA's analysis but not in the Applicant's analysis.*
CI = confidence interval

90% CI for the ORR ratio at 24 weeks lies within the equivalence margins (0.81-1.24)

Clinical Safety

	MYL-1401O N=247 N (%)	EU-Herceptin N=246 N (%)
Patients with all grade TEAEs	241 (97.6)	239 (97.2)
Patients with Grade ≥ 3 TEAEs	161 (65.2)	162 (65.2)
Patients with serious TEAEs	97 (39.3)	91 (37.0)
Patients with treatment-related TEAEs	103 (41.7)	88 (35.8)
Patients with TEAEs leading to withdrawal from study	9 (3.6)	9 (3.7)
Total patient deaths	7 (2.8)	5 (2.0)

TEAE=treatment-emergent adverse event

Clinical Safety

- Adverse events of interest (cardiac toxicities, infusion reactions, pulmonary toxicities) were observed in both arms with no meaningful differences
- Immunogenicity similar between the two arms
- Overall: no meaningful safety differences between MYL-1401O and EU-Herceptin, which supports a demonstration of no clinically meaningful differences between MYL-1401O and US-Herceptin

Extrapolation

Proposed indications:

Adjuvant Breast Cancer

HER2 overexpressing node positive or node negative breast cancer:

- as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
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Support for Extrapolation

- Mechanism of action is the same across indications
- Similarity has been demonstrated with regard to:
 - Analytical attributes
 - Pharmacokinetics
 - Immunogenicity
 - Efficacy
 - Safety

Summary of FDA Findings

Biosimilarity

- Highly similar to reference product, notwithstanding minor differences in clinically inactive components
- No clinically meaningful differences in safety, purity, and potency from the reference product

Summary of FDA Findings

- Totality of analytical data supports demonstration of highly similar, notwithstanding minor differences in clinically inactive components.
- Clinical data, including pharmacokinetics, efficacy, safety, and immunogenicity support no clinically meaningful differences.

Overall Conclusion

- A scientific bridge has been established between EU-Herceptin, US-Herceptin, and MYL-1401O.
- Totality of the evidence supports a demonstration of biosimilarity between MYL-1401O and US-Herceptin.
- Extrapolation to all indications is supported by the scientific understanding of the mechanism of action across indications and demonstration of biosimilarity.

Discussion Points

1. Please discuss whether the evidence supports a demonstration that “MYL-1401O” is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components.
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